cardiaques précédemment exclus, entraîne régulièrement une hypertension passagère accompagnée de fibrillation et d'arythmie cardiaque. Ces troubles peuvent être diminués, raccourcis et même supprimés par un traitement préalable avec le No. 11 081 5–10 mg/kg i.v. (Fig. 2).

Dans ces deux tests chez l'animal entier, l'α-fagarine produit un effet analogue à des doses semblables, tandis que la procaine semble moins active, surtout contre l'arythmie due à l'adrénaline + cyclopropane. Par contre, la nouvelle substance est bien active per os à la dose de 50 mg/kg, ce qui contraste avec l'irrégularité de l'effet per os de la procaine.

J. TRIPOD, M. SPILLMANN et K. HOFFMANN

Laboratoires scientifiques de CIBA, Société Anonyme, Bâle, le 26 février 1954.

Summary

A new synthetic phenyl-ethyl-amine derivative, the 2-[N-(3',4'-methylen-dioxyphenylethyl)-methylaminomethyl]-tetrahydrofuran, No. 11 081, exhibits a strong protective effect against cardiac fibrillation and arrhythmias produced by various experimental methods: against fibrillation due to aconitine 3×10^{-8} on the isolated cat's heart, it is active in a concentration of 10^{-6}–2×10^{-6}. Against cardiac arrhythmias produced in the cat by adrenaline + $CHCl_3$ or cyclopropane, it shows a protective effect by 5–10 mg/kg i.v. and even perorally by 50 mg/kg. In these tests, the antifibrillatory activity of the new compound seems to be roughly the same as that of α-fagarine, and higher than that of procaine.

Neurosecretion and Anterior Pituitary in the Dog[1]

It has been shown in a variety of vertebrates that the stainable granules which are produced by neurosecretory cells in the hypothalamus pass along the axons through the pituitary stalk into the posterior lobe. There they are stored in nerve endings surrounding blood vessels into which the granules are released. This neurosecretory material contains the posterior lobe hormones. The posterior pituitary can be depleted of this material in experimental animals by subjecting them to conditions causing the release of posterior lobe hormones. The dehydrated organism, for instance, in an effort to conserve body water, reduces urinary output by using up large amounts of antidiuretic hormone. The posterior pituitaries of such animals contain only small quantities of neurosecretory material. As soon as adequate amounts of water are again available and the requirements for antidiuretic hormone return to normal, the neurosecretory substance quickly re-accumulates in the perivascular nerve endings of the posterior pituitary[2].

It appears that the vessels of the posterior pituitary are not the only outlets for this material. In amphibians, granules which stain the same way as those stored in the posterior pituitary, can be traced along nerve fibers from the neurosecretory cells of the hypothalamus to the median eminence in which the fibers end around capillaries. Here the neurosecretory material is deposited in a perivascular pattern similar to that seen in the posterior lobe[1]. The capillaries of the median eminence are connected with vessels which supply another capillary bed in the anterior lobe of the pituitary[2]. In analogy to the hepatic portal system, these vascular connections between median eminence and anterior pituitary have been called portal vessels. Corresponding relationships obtain in reptiles[3]. In birds, nerve fibers descending from the neurosecretory cells of the hypothalamus toward the posterior pituitary form loops which reach capillaries connected with the portal vessels. These nerve fibers carry neurosecretory material; the loops could facilitate the transfer of this material from the nerve fibers to the capillaries[4].

With respect to mammals there is some disagreement as to whether or not neurosecretory material is found in nerves ending at the capillaries in the peripheral zone of the infundibular stalk. Although a number of observers have reported accumulations of neurosecretory material around the vessels in the median eminence[5], others deny their occurrence[6].

Since contradictory statements refer even to the same species, namely the dog, the question has been re-examined in a large material of dogs, both purebred (greyhounds and basset hounds) and mongrels of different ages.

The animals were anesthesized with nembutal (pentobarbital sodium). A cannula was tied into the ascending aorta; the descending aorta and axillary arteries were clamped off. The head was perfused with saline followed by ZENKER's fluid to which, in the course of the perfusion, 5% formalin was added. The hypothalamus with the attached hypophysis was removed, fixed in Zenker-formol for another 12 to 24 h, washed, and carried through the alcohol series, methylbenzoate and benzene into paraffin for embedding. Serial sections of 5 and 7 μ thickness were stained by the chrome hemato-

[1] Dedicated to Professor FRIEDRICH BALTZER, University of Berne, Switzerland, on the occasion of his 70th birthday, March 12, 1954.

[1] These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Colorado, Nr. 112-335.

[2] R. ORTMANN, Klin. Wschr. *28*, 449 (1950); Z. Zellforsch. *36*, 92 (1951). – W. HILD, Virchow's Arch. *319*, 526 (1951); Acta neuroveg. *3*, 81 (1951); Z. Zellforsch. *37*, 301 (1952). – W. HILD und G. ZETLER, Exper. *7*, 189 (1951); Arch. exp. Path. Pharmakol. *213*, 139 (1951); Klin. Wschr. *30*, 433 (1952); Dtsch. Z. Nervenheilk. *167*, 205 (1952); Z. ges. exp. Med. *120*, 236 (1953); Pflügers Arch. *257*, 169 (1953). – F. STUTINSKY, C. r. Soc. Biol. (Paris) *146*, 1691 (1952). – TH. F. LEVEQUE and E. SCHARRER, Endocrinology *52*, 436 (1953).

[3] Unpublished observations.

[4] J. BENOIT et I. ASSENMACHER, Pubbl. Staz. Zool. *24* (Suppl.), 27 (1954).

[5] W. BARGMANN, W. HILD, R. ORTMANN, and TH. H. SCHIEBLER, Acta neuroveg. *1*, 233 (1950). – F. STUTINSKY, C. r. Soc. Biol. Paris *145*, 367 (1951). – W. HILD, Z. Zellforsch. *37*, 301 (1952). – W. BARGMANN, Geburtsh. Frauenheilk. *13*, 193 (1953). – S. L. PALAY, Am. J. Anat. *93*, 107 (1953). – G. A. DRAGER, J. Comp. Neur. *99*, 75 (1953). – A. R. ROTHBALLER, Anat. Rec. *115*, 21 (1953). – W. BARGMANN, Verhandl. Anat. Ges., Anat. Anz., Ergänzungsh. zu Bd. *100*, 30 (1954). – B. HANSTRÖM describes a granular material stainable with azan, but not with GOMORI's chrome hematoxylin in the median eminence of the coney, *Procavia capensis* (Arkiv för Zoologi, *4*, 187 [1952]) and the TASMANIAN ant-eater, *Tachyglossus setosus* (Z. Zellforsch. *39*, 241 [1953]). He discusses (Arkiv för Zoologi *6*, 97 [1953]) the possibility that this material is carried via the portal vessels into the anterior pituitary and thus plays a role in its humoral control. This material could be produced by cells of tuber nuclei whose fibers end in the median eminence. It will be of great interest to determine whether the same material stains differently in different species or whether the median eminence actually receives different kinds of neurosecretory material from different groups of nerve cells in the hypothalamus.

[6] J. CHRIST, Dtsch. Z. Nervenheilk. *165*, 340 (1951). – H. NOWAKOWSKI, Dtsch. Z. Nervenheilk. *165*, 261 (1951). – H. SPATZ, Acta neuroveg. *3*, 5 (1951). – H. KNOCHE, Acta Anat. *18*, 208 (1953).

xylin-phloxine method of GOMORI as recommended by BARGMANN[1].

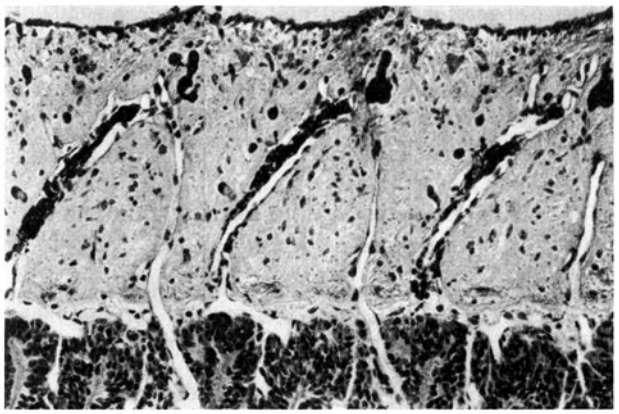

Fig. 1.—Three consecutive sections through the pituitary stalk and anterior pituitary of a bassethound (3½ months old). Masses of neurosecretory material surround the portal vessels. Vascular perfusion with Zenker-formol, paraffin, 5μ, GOMORI's chrome-hematoxylin-phloxin stain, photomicrograph, magnification × 325.

The stainability of the neurosecretory material in the hypothalamic-hypophyseal system with chrome hematoxylin, while not specific, is highly selective and permits the identification of even small amounts of this substance. As Figures 1 and 2 show, neurosecretory material can be observed in the dog along the vessels which extend into the peripheral zone of the pituitary stalk, and which are continuous with the blood vessels of the anterior pituitary. While this localization of neurosecretory material has been observed in a number of adult dogs, it is particularly conspicuous in young animals.

Fig. 2.—Neurosecretory material along wall of a portal vessel in the pituitary stalk. Material and technique as in Figure 1. Magnification × 950.

If neurosecretory granules are actually released into the blood vessels to be carried to the anterior pituitary, one might expect increased accumulation of this material if it loses its outlet as a result of hypophysectomy. This is indeed the case in hypophysectomized rats in which the portal vessels are surrounded by much larger quantities of neurosecretory material than is seen normally[1]. The same phenomenon has been observed in a clinical case of pituitary infantilism in which the pituitary had been destroyed in childhood. The patient died at the age of 60 years. Sections of the median eminence showed capillary loops in the midst of numerous granules and droplets which stained blue with chrome hematoxylin[2].

Present methods indicate that the neurosecretory cells of the mammalian hypothalamus produce only one substance which is stainable with chrome hematoxylin and contains the posterior lobe hormones. If this substance is indeed carried to the anterior lobe via the portal vessels it could play a role in the control of the release of anterior lobe hormones as has been proposed by several investigators (BARGMANN, PALAY, DRAGER, and others)[3]. In this case one would have to assume either that the neurosecretory material contains active principles in addition to the posterior lobe hormones, or that the latter stimulate the cells of the anterior pituitary. The second possibility would explain certain tie-ups between anterior and posterior lobe hormones. Stress, for instance, causes the release of both ACTH and antidiuretic hormone[4]. If posterior lobe hormones circulating in the anterior pituitary can elicit the discharge of ACTH, prolonged administration of posterior lobe extracts should result in a hypertrophy of the adrenal cortex. Such an effect has been observed[5]. Corresponding relationships appear to exist between the posterior lobe hormones and the gonadotropic hormones of the anterior pituitary. Thus optical stimuli which presumably are transmitted from the eye to the hypothalamus, may result in the discharge from the posterior pituitary of hormones affecting water excretion[6] as well as the release from the anterior pituitary of gonadotropic

[1] W. BARGMANN, Z. Zellforsch. *34*, 610 (1949). – Mikroskopie (Wien) *5*, 289 (1950).

[1] F. STUTINSKY, C. r. Soc. Biol. (Paris) *145*, 367 (1951). – T. F. LEVEQUE, Unpublished observations.

[2] H. ORTHNER, Acta neurovegetativa *3*, 50 (1951). – H. ORTHNER and T. H. SCHIEBLER, Arch. Psychiat. Nervenkrankh. *186*, 59 (1951).

[3] W. BARGMANN, W. HILD, R. ORTMANN, and TH. H. SCHIEBLER, Acta neuroveg. *1*, 233 (1950). – F. STUTINSKY, C. r. Soc. Biol. Paris *145*, 367 (1951). – W. HILD, Z. ZELLFORSCH. *37*, 301 (1952). – W. BARGMANN, Geburtsh. Frauenheilk. *13*, 193 (1953). – S. L. PALAY, Am. J. Anat. *93*, 107 (1953). – G. A. DRAGER, J. Comp. Neur. *99*, 75 (1953). – A. R. ROTHBALLER, Anat. Rec. *115*, 21 (1953). – W. BARGMANN, Verhandl. Anat. Ges., Anat. Anz., Ergänzungsh. zu Bd. *100*, 30 (1954). – B. HANSTRÖM describes a granular material stainable with azan, but not with GOMORI's chrome hematoxylin in the median eminence of the coney, *Procavia capensis* (Arkiv för Zoologi *4*, 187 [1952]) and the TASMANIAN ant-eater, *Tachyglossus setosus* (Z. Zellforsch. *39*, 241 [1953]). He discusses (Arkiv for Zoologi *6*, 97 [1953]) the possibility that this material is carried via the portal vessels into the anterior pituitary and thus plays a role in its humoral control. This material could be produced by cells of tuber nuclei whose fibers end in the median eminence. It will be of great interest to determine whether the same material stains differently in different species or whether the median eminence actually receives different kinds of neurosecretory material from different groups of nerve cells in the hypothalamus.

[4] M. A. HAYES and F. A. COLLER, Surg., Gynecol. Obst. *95*, 142 (1952). – I. A. MIRSKY, R. MILLER, and M. STEIN, Psychosomatic Med. *15*, 574 (1953). – I. A. MIRSKY, M. STEIN, and G. PAULISCH, Endocrinology *54*, 491 (1954)). – ST. KARÁDY, J. S. L. BROWNE, and H. SELYE, Quart. J. Exp. Physiol. *28*, 23 (1938).

[5] R. C. MOEHLIG and E. A. OSIUS, Ann. Int. Med. *4*, 578 (1931).

[6] E. M. BOYD and F. M. YOUNG, Endocrinology *27*, 137 (1940). – E. M. BOYD, B. K. LEE, and M. E. T. STEVENS, Endocrinology *32*, 27 (1943). – D. HOFMANN-CREDNER, Helv. med. Acta [A] *20*, 1 (1953). – F. HOLLWICH, Münch. Med. Wschr. *94*, 1057 (1952).

hormones[1]. Accordingly, lesions in the hypothalamus and the median eminence of the pituitary stalk which cause diabetes insipidus also disturb hypophyseal gonadotropic functions[2]

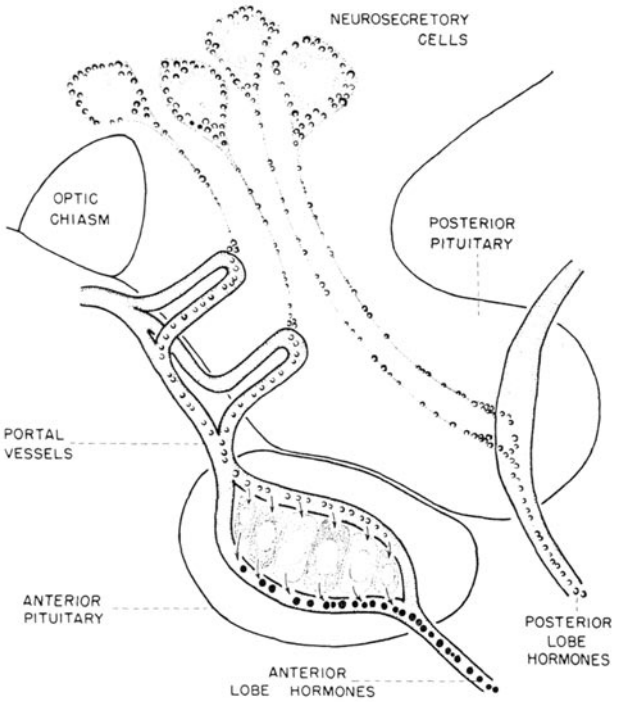

Fig. 3.—Diagram to illustrate a possible passage of neurosecretory material via portal vessels to the anterior pituitary and its hypothetical role in the release of anterior lobe hormones such as ACTH and gonadotropins.

Such relationships could mean that in the release of both posterior and anterior lobe hormones, the same system of neurosecretory cells plays a role in a manner illustrated schematically in Figure 3. However, in mammals there is as yet no direct experimental evidence to support this hypothesis. In fact, ZUCKERMAN[3] concludes from experiments in ferrets that there is no such relationship. On the other hand, the observations of BENOIT and ASSENMACHER[4] in birds strongly support it. Clearly, this problem deserves further study.

E. SCHARRER

Department of Anatomy, University of Colorado, School of Medicine, Denver, Colorado, USA, April 4, 1954.

Zusammenfassung

Die Ablagerung von neurosekretorischem Material in der unmittelbaren Umgebung von Blutgefässen im Hypophysenstiel, die mit Gefässen des Vorderlappens in Verbindung stehen, wird beim Hund beschrieben. Aus diesem Befund wird auf die Möglichkeit geeshlossen, dass die von den Zellen der Nuclei supraopticus und paraventricularis produzierte neurosekretorische Substanz nicht nur in die Gefässe des Hypophysenhinterlappens abgeschieden wird und im Körperkreislauf die sogenannten Hinterlappenhormone abgibt, sondern auch in den Pfortaderkreislauf des Vorderlappens gelangt und dort die Absonderung von Hormonen, wie zum Beispiel ACTH, bewirkt.

[1] D. S. FARNER, L. R. MEWALDT, and S. D. IRVING, Biol. Bull. *105*, 434 (1953). – M. GALGANO and V. MAZZI, Riv. Biol. *43*, 21 (1951). – J. BENOIT, I. ASSENMACHER, and F. X. WALTER, C. r. Soc. Biol. Paris *144*, 573 (1950). – J. BENOIT, F. X. WALTER, and I. ASSENMACHER, J. de Physiol. *42*, 537 (1950). – C. r. Soc. Biol. Paris *144*, 1206 (1950). – J. BENOIT and I. ASSENMACHER, J. de Physiol. *43*, 643 (1951).

[2] F. L. DEY, C. FISHER, C. M. BERRY, and S. W. RANSON, Am. J. Physiol. *129*, 39 (1940).

[3] S. ZUCKERMAN, Pubbl. Staz. Zool. *24* (Suppl.), 21 (1954).

[4] J. BENOIT and I. ASSENMACHER, Arch. Anat. Micr. Morph. Exp. *42*, 334 (1953).

Activité gonadotrope d'un extrait d'urines de femmes en ménopause

Contrairement à la gonadotrophine choriale (HCG, Human Chorionic Gonadotrophin), les actions biologiques des gonadostimulines humaines d'origine hypophysaire sont encore très peu connues. En résumant la littérature sur l'activité gonadotrope des urines provenant de femmes en ménopause physiologique ou artificielle («HMG», Human Menopausal Gonadotrophins[1]), EVANS et SIMPSON[2] arrivent à la conclusion que le facteur FSH (Follicle Stimulating Hormone) prédomine nettement. Les extraits urinaires stimulent en effet chez le rat hypophysectomisé la croissance des follicules ovariques et la prolifération de l'épithélium séminal. D'après les auteurs cités, seules des doses très élevées entraîneraient par contre le rétablissement des cellules interstitielles atrophiées à la suite de l'hypophysectomie ou chez la rate intacte et impubère la formation de corps jaunes. Les effets caractérisant l'action du facteur ICSH (Interstitial Cell Stimulating Hormone) seraient donc discrets par rapport à ceux du facteur FSH.

GREEP et JONES[3] affirment qu'une activité d'ICSH est facilement démontrée dans les urines de femmes ménopausées tout en maintenant qu'il y en a peu et que le facteur FSH prédomine. Ils ont obtenu chez des rats impubères hypophysectomisés aussi bien une augmentation des poids des testicules, des vésicules séminales et des prostates ventrales, qu'une augmentation des poids ovariques et utérins et la formation de corps jaunes.

Ces résultats sont opposés aux observations de SCHULER[4] qui a injecté à des rats hypophysectomisés des extraits urinaires provenant de trois femmes dont l'âge dépassait 60 ans. Il n'a pas constaté d'augmentation des poids ovariques et utérins qui aurait témoigné de la présence du facteur FSH, par contre un degré de lutéinisation comparable à une activité de 10–20 U.I. de HCG par litre d'urine.

Nous avons tâché de contribuer, par de nouveaux faits expérimentaux, à la solution du problème en examinant l'activité gonadotrope d'un extrait[5] intitulé «HMG» et préparé à partir d'une grande quantité

[1] Nous employons dans ce travail les termes, critères et méthodes recommandés par F. BENZ (Bâle), R. BORTH (Genève), J. B. BROWN (Edimbourg), W. R. BUTT (Birmingham), A. C. CROOKE (Birmingham), E. DICZFALUSY (Stockholm), J. A. LORAINE (Edimbourg), B. LUNENFELD (Genève), W. SCHULER (Bâle) et H. DE WATTEVILLE (Genève) lors d'une réunion à la Maternité de Genève, du 26 au 28 août 1953.

[2] H. M. EVANS et M. E. SIMPSON, *Physiology of the Gonadotrophins* dans G. PINCUS et K. V. THIMANN, *The Hormones*, vol. 2 (Academic Press, New York 1950).

[3] R. O. GREEP et I. C. JONES, Recent Progr. Horm. Res. *5*, 242 (1950).

[4] W. SCHULER, Helv. physiol. pharmacol. Acta [C] *5*, 47 (1947).

[5] Nous remercions vivement MM. le professeur J. H. GADDUM et le Dr J. A. LORAINE (Edimbourg) qui ont bien voulu mettre à notre disposition un échantillon de cet extrait préparé par la Maison ORGANON (Newhouse, Ecosse).